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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/609,233	06/27/2003	Imtiaz Chaudry	048765/277090	8210
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ALSTON & BIRD LLP BANK OF AMERICA PLAZA 101 SOUTH TRYON STREET, SUITE 4000 CHARLOTTE, NC 28280-4000			EXAMINER HAGHIGHATIAN, MINA	
			ART UNIT	PAPER NUMBER
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			06/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/609,233	Applicant(s) CHAUDRY, IMTIAZ	
	Examiner Mina Haghighatian	Art Unit 1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 April 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5,10-30 and 32-69 is/are pending in the application.
- 4a) Of the above claim(s) 6,7,10,11,17-20,22-24,33,35-37 and 41-50 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5,12-16,21,25-30,32,38-40 and 51-69 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>4/17/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/17/07 has been entered.

Claims 15, 27, 38, 51 have been amended and no new claims added. Claims 6-7, 10-11, 17-20, 22-24, 33, 35-37 and 41-50 remain withdrawn and claims 3-4, 8-9 and 31 remain cancelled. Accordingly, claims **1,2, 5, 12-16, 21, 25-30, 32, 38-40, 51-69** are under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,2, 5, 12-16, 21, 25-30, 32, 38-40, 51-69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed

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invention. Claims 1, 10, 27, 38, 51 recite concentration ranges for the active agents that have no support in the specification. Specification, on pages 14-16 recite various concentration ranges, however there is no mention of 0.1 mg/ml to 15 mg/ml, 1 mg/ml to 10 mg/ml or 0.15 mg/ml to 15 mg/ml as suitable ranges. In fact concentrations of 0.1mg/ml and 0.15 mg/ml are not listed at all and 1 mg/ml is only cited as an upper limit and not a lower limit.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 12-14, 16 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Kiechel et al (4,885,305).

Kiechel discloses nasal compositions comprising as active agent a calcium antagonist together with a non-toxic pharmaceutically acceptable nasal carrier therefor (see abstract). Preferred calcium antagonists include **felodipine, fluordipine, nicardipine, nifedipine**, etc. Most preferred is nicardipine (see col. 1, lines 60-67)

The composition is preferably in the form of an aqueous solution. Alternatively it may be in the form of a **suspension** or an **emulsion** (col. 2, lines 20-25). The said formulations may also comprise pharmaceutical excipients such as anti-oxidants,

preservatives (conservation agents), etc. Such excipients include sodium benzoate, benzalkonium chloride, etc (see col. 2, lines 32-54). It is preferred to administer a nasal spray which is **isotonic** with respect to the ciliary mucus (col. 2, lines 60-68).

The formulations are said to have a **pH** of between 3.5 and 9, and preferably from **3 to 4**. The desired pH may be achieved by means of the presence of a buffer system, e.g. acetic acid/sodium acetate, etc (see col. 3, lines 1-13). The said formulations are sterilized under conventional conditions and packaged in conventional manner in a nasal applicator adapted to produce a spray of the composition. The formulation may be packaged in unit doses in ampoules (see col. 3, lines 14-35). The formulation has a suitable concentration range of the active agent from about 0.1 to about 0.45% or 1 to 4.5 mg/ml (see col. 3, lines 43-59). The nasal formulations taught by Kiechel are said to be useful for the same indications as the systemic administration, i.e. cardiac disorders, **hypertension**, etc (col. 3, lines 61-67).

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 15, 25-30, 32, 34, 38-40 and 51-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kiechel et al (4,885,305) in view of Mead et al (6,608,054).

Kiechel et al, discussed above lacks disclosure on adding complexing agents.

Mead et al teach pharmaceutical compositions based on anticholinergics and endothelin antagonists, processes for preparing them and their use in the treatment of respiratory tract disease (see abstract). The said disorders include pulmonary hypertension (see col. 2, lines 56-64). Mead discloses that the formulation preferably have a **pH of from 2 to 7**, which is obtained by addition of acids or a mixture of acids. Preferably acids which have other properties in addition to their acidifying qualities, e.g. complexing agent, antioxidant, etc. The addition of editic acid (EDTA) or one of the known salts thereof, sodium edentate, as stabilizer or complexing agents is unnecessary. Other embodiments may contain this compound or these compounds. In a preferred embodiment the content based on sodium edetate is less than 100mg/100ml. Generally, inhalable solutions in which the content of **sodium edetate** is from 0 to 10mg/ml are preferred (col. 9, lines 1-35). Preferred formulations contain, in addition to the solvent water and the combination of active substances, only benzalkonium chloride and sodium edetate (col. 10, lines 8-11).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of Kiechel et al on spray formulations comprising active agents and carriers packaged in unit doses for treating disorders such as hypertension with the teachings of Mead et al on inhalable formulations comprising active agents, carriers and complexing agents with reasonable

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expectations of successfully preparing safe, stable formulations for effective inhalation therapy.

Claim 1,2, 5, 12-16, 21, 25-30, 32, 38-40, 51-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Williams et al (5,554,610) in view of in view of Azria et al (5,759,565) or alternatively in view of Schwarz (US 20010031738) and further in view of Mead et al (6,608,054).

Williams teaches a **method for the treatment of pulmonary hypertension** comprising administering to a mammal an effective amount of a vasodilator. The formulations can treat primary and secondary pulmonary hypertensions (col. 2, lines 1-6). The administration is preferably **through inhalation**. **Unit doses** comprising 0.01 to 50 mg and preferably from 0.1 to 10 mg of the compound are normally administered one to 4 times a day. The compositions are prepared by admixture and can be in a solution or **suspension** form (col. 2, lines 16-48, 60-67). One preferred composition comprises in an **aqueous suspension** form, additives such as suspending agents, preservatives, carriers and buffers. The said agents include **propylene glycol, ethyl alcohol**, etc. The compositions for administration to the respiratory tract are presented as **snuff** or an aerosol or solution for a **nebulizer** or as a microfine powder for insufflation, alone or in combination with an inert carrier. In other preparations, such as for parenteral administration, the fluid unit dose forms are prepared containing the compound and a **sterile** vehicle, undergo **filter sterilization** and filled into a vial. The

compositions are typically accompanied by written or printed directions for use (see col. 3, lines 1-66).

Williams also discloses that suitable vasodilators include **calcium channel blockers** such as **nifedipine** (col. 4, lines 20-21). A particularly favored pharmaceutically acceptable composition is an inhalation composition, suitably in unit dosage form (col. 4, lines 37-40). Williams lacks disclosure on pH levels and isotonicity of the formulations and addition of complexing agents.

Azria et al teach compositions for nasal administration. It is disclosed that "generally, for **nasal** administration a mildly acid pH will be preferred. Preferably the compositions of the invention have a **pH of from about 3 to 5**, most preferably 3.5 to 4.5. Adjustment of the pH is achieved by addition of an appropriate acid, such as hydrochloric acid. The compositions of the invention should also possess an appropriate isotonicity and viscosity" (see col. 4, lines 15-25). The formulations are filtered using a 0.2 μm filter (see col. 8, lines 30-38).

Schwarz teaches a method of treating pulmonary hypertension by inhalation. It is disclosed that the aerosol **suspensions** can be aerosolized by a metered dose inhaler ([0049]) or with a pressure-driven **aerosol nebulizer** or an **ultrasonic nebulizer**. The suitable carrier is typically water and most preferably **sterile water**, and preferably made isotonic. Optional preservatives, **pH-adjusting agents**, **buffering agents** and surfactants are included (see [0041] and [0051]). The doses of the active compounds

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may be provided as **one or several prepackaged units** (see [0059]). It is also disclosed that suitable formulations comprise **citrate** or bis/tri buffer (**pH 6**) (see [0045]).

Mead et al, discussed above, discloses formulations for inhalation comprising complexing agents.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to have implemented teachings of Azria et al on nasal administration of formulations or alternatively Schwarz on inhalation of formulation for treating pulmonary hypertension, with the general teachings and formulations of Williams et al and the formulations of Mead et al with a reasonable expectations of successfully preparing efficient and easy to use formulations that treat pulmonary hypertension in patients. In other words Williams et al are teaching the inhalation of vasodilators for treating pulmonary hypertension. Williams et al disclose the use of buffers for their formulations, however, they are silent with regards to specific pH levels and isotonicity of the formulations. It is well known in the art that mucosal membranes tolerate certain isotonicity and pH levels. It is also well known in the art that pH levels are adjustable by use of acids, bases or buffers. Azria et al and Schwarz have been provided as supportive art showing that it is known in the art that an isotonic formulation having pH levels of 3-8 are suitable for inhalation and nasal administrations. Mead et al is also supportive art showing that adding complexing agents to formulations are known. Thus it is clearly shown that all limitations of the instant claims are met by Williams in

view of Azria et al or in the alternative in view of Schwarz and Mead et al or knowledge generally available to one of ordinary skill in the art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims **1,2, 5, 12-16, 21, 25-30, 32, 38-40, 51-69** are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2, 5-7, 10-14, 16, 21 and 25-26 of copending Application No. 11/316,458 (US 20060104913). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are anticipated by the reference claims. The instant claim 1 and the reference claim 1 both recite an inhalable formulation for the treatment of pulmonary hypertension comprising from 0.1 to 15

mg/ml of a reducing agent such as calcium channel blocker wherein the formulation is free of a compound selected from the group consisting essentially of i) an anti-EMAP II antibody, ii) antisense EMAP II oligonucleotide and iii) EMAP II antagonist and wherein the formulations have a pH of from 3 to 8. The difference is that instant claim 1 contains a further negative proviso wherein the formulation is not a liposome. The remaining claims are also anticipated by the reference claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments

Applicant's arguments filed 04/17/07 have been fully considered but they are not persuasive. Applicant argues that the previous Office Action asserted that Williams inherently teaches or suggests the current concentration ranges. This is not correct because Office Action did not attempt to establish inherency. It was stated that it would have been **obvious** to one of ordinary skill in the art to have modified Williams's disclosure of the amount of active in the unit dose to obtain a concentration range for the formulation. Williams discloses a unit dose that can be in a liquid form to contain from 0.01 to 50 mg of the active compound. Such unit doses typically contain from 1 to 5 ml of the liquid formulation. Therefore a concentration range for the said unit dose would be in mg/ml.

Applicant argues that Azria is silent with regards to the reducing agents and the complexing agents. This is not persuasive because It has been shown that Williams

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teaches inhalable formulations comprising reducing agents for treating pulmonary hypertension. Azria was brought in to teach what was missing which is the pH levels suitable for inhalation or nasal formulations.

Applicant argues that Schwarz is directed to formulations for inhibiting endothelial-monocyte activating polypeptide II (EMAP II). This is not persuasive because Schwarz also teaches inhalable formulations comprising reducing agents and liquid carriers for inhalation formulations. Schwarz was relied upon for its teachings of the pH levels and isotonicity of the formulation and one of ordinary skill in the art would be able to make and use the Schwarz's formulations without the EMAP II compounds.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mina Haghighatian whose telephone number is 571-272-0615. The examiner can normally be reached on core office hours.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

A handwritten signature in black ink, appearing to read 'Mina Haghighatian', with a large, stylized loop at the end.

Mina Haghighatian
Patent Examiner
June 13, 2007